

Multimodal microstructure imaging: joint T2-relaxometry and diffusometry to estimate myelin, intracellular, extracellular, and cerebrospinal fluid properties

Marco Pizzolato¹, Erick Jorge Canales-Rodríguez^{1,2}, Alessandro Daducci^{1,2,3}, and Jean-Philippe Thiran¹

¹Signal Processing Lab (LTS5), École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland, ²Radiology Department, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland, ³Computer Science Department, University of Verona, Verona, Italy

Synopsis

We propose a multimodal joint estimation that aims at exploiting the complementary information of diffusion and multi-echo spin echo data to disentangle the contributions and properties of the main tissue microstructure compartments. We recovered T₂, diffusion coefficient, and volume fractions values of myelin, intracellular, extracellular, and cerebrospinal fluid compartments within an *ex vivo* spinal cord sample by means of diffusometry and relaxometry. A g-ratio map was also calculated.

Introduction

Magnetic Resonance Imaging (MRI) of nervous tissue microstructure is a rather complex task due to the fact that one modality can be sensitive to some tissue properties being almost blind to others. This is the case of multicomponent analysis of multi-echo spin echo data, i.e. T₂-relaxometry¹, which allows estimating the volume fraction and T₂ values of myelin and cerebrospinal fluid (csf), but that hardly allows distinguishing between the contributions of intracellular and extracellular compartments. Similarly, diffusometry¹ - the multicomponent analysis of diffusion data - gives information about intracellular, extracellular, and cerebrospinal fluid compartments, but has little sensitivity to myelin due to its characteristic T₂, too short compared to typical echo times (TE) used for PGSE² sequences.

We propose to jointly perform and estimate T₂-relaxometry and diffusometry in a synergic manner to disentangle the T₂ value, diffusion coefficient, and volume fraction of each compartment separately. To this end, we propose a non-linear multimodal approach. We show results on *ex vivo* spinal cord data³, collected in a favorable experimental setup where diffusion data is acquired along the direction perpendicular to axons. However, the multimodal approach could be extended to general relaxometry and diffusion MRI acquisitions previous formal modeling. In the following, we present the proposed method, the results, and, our discussion and conclusion.

Methods

The *ex vivo* spinal cord dataset³ contains a 64x64 voxels slice with a multi-echo spin echo acquisition (32 echoes, $ESP/TR = 10ms/3s$, 8 averages) and a 1-dimensional PGSE acquisition perpendicular to the spinal cord longitudinal direction, from which we selected 50 samples with $TE_{diff} = 47ms$ equally distributed in b-value, b , with maximum gradient strength $G_{max} = 0.6 T/m$, pulse duration $\delta = 8ms$, and separation $\Delta = 25ms$.

We propose to jointly estimate microstructure parameters from the two modalities, precisely the transverse relaxation time T₂, diffusion coefficient d , and volume fraction f for the myelin, *mye*, intracellular, *int*, extracellular *ext*, and cerebrospinal fluid *csf* compartments:

$$S(TE, b, K) = K \sum_{i \in \{mye, int, ext, csf\}} f_i e^{-\frac{TE}{T_2^i}} e^{-bd_i} \quad s. t. \quad \sum_{i \in \{mye, int, ext, csf\}} f_i = 1$$

where S is the description of the T₂-weighted diffusion signal, and K is a constant. To compensate for modality-related instrumental differences, different constants are used: if $Y_d(b)$ and $Y_{me}(TE)$ are the acquired diffusion and multi-echo signals, then we set $K_{me} = \hat{Y}_{me}(0)$ for multi-echo and $K_d \approx K_{me} \frac{\hat{Y}_d(0)}{\hat{Y}_{me}(TE_{diff})}$ for diffusion. Estimation of constants was performed after non-negative least squares spectroscopy¹, which was also used to initialize the non-linear routine minimizing the following *joint* objective function

$$\frac{\sum_j^{N_d} [S(TE_{diff}, b_j, K_d) - Y_d(b_j)]^2}{N_d} + \frac{\sum_k^{N_{me}} [S(TE_k, 0, K_{me}) - Y_{me}(TE_k)]^2}{N_{me}}$$

N_d and N_{me} being the number of samples of the related signals.

Results

As the non-linear problem is hard to solve, the optimization was constrained imposing large bounds on parameters, based on visual inspection of non-parametric spectroscopy results. Moreover, due to the low sensitivity of diffusion data to myelin at this echo-time, we neglected its contribution for the first addend of the objective function. Similarly, due to low separability between intra- and extracellular transversal relaxation times with multi-echo data, we approximated $T_i = T_e = T_{ie}$.

In Fig. 1 we show the estimated quantities for the myelin, intracellular, extracellular, and cerebrospinal fluid compartments, obtained with the proposed joint estimation method. The average values for white matter are $f_{mye} = .35$, $f_{int} = .42$, $f_{ext} = .22$, $T_2^{mye} = 26ms$, $T_2^{ie} = 87ms$, $d_{int} = 1.6e^{-11} m^2/s$, $d_{ext} = 1.5e^{-10} m^2/s$. In the cerebrospinal fluid found in the spinal cord canal the average values are $T_2^{csf} = 411ms$, and $d_{csf} = 1.08e^{-9} m^2/s$.

In Fig. 2 we report the g-ratio⁴ map calculated with results shown in Fig. 1, and the related histogram. The average value is 0.73.

Discussion

The proposed multimodal joint estimation aims at exploiting the complementary information of diffusion and multi-echo spin echo data to disentangle the contributions and properties of the main microstructure compartments. Results in Fig. 1 show expected proportions of intracellular, extracellular, and myelin volume fractions. Cerebrospinal fluid is correctly detected in the spinal cord canal, and around the sample. T_2 values are correctly ordered and match expected values. Also the diffusion coefficients well distinguish different compartments, which have values approximately separated by one order of magnitude. Finally, the g-ratio map in Fig. 2 reports values perfectly aligned with literature⁵. Despite the presence of partially non-smooth regions, maps look substantially regular and coherent.

Conclusion

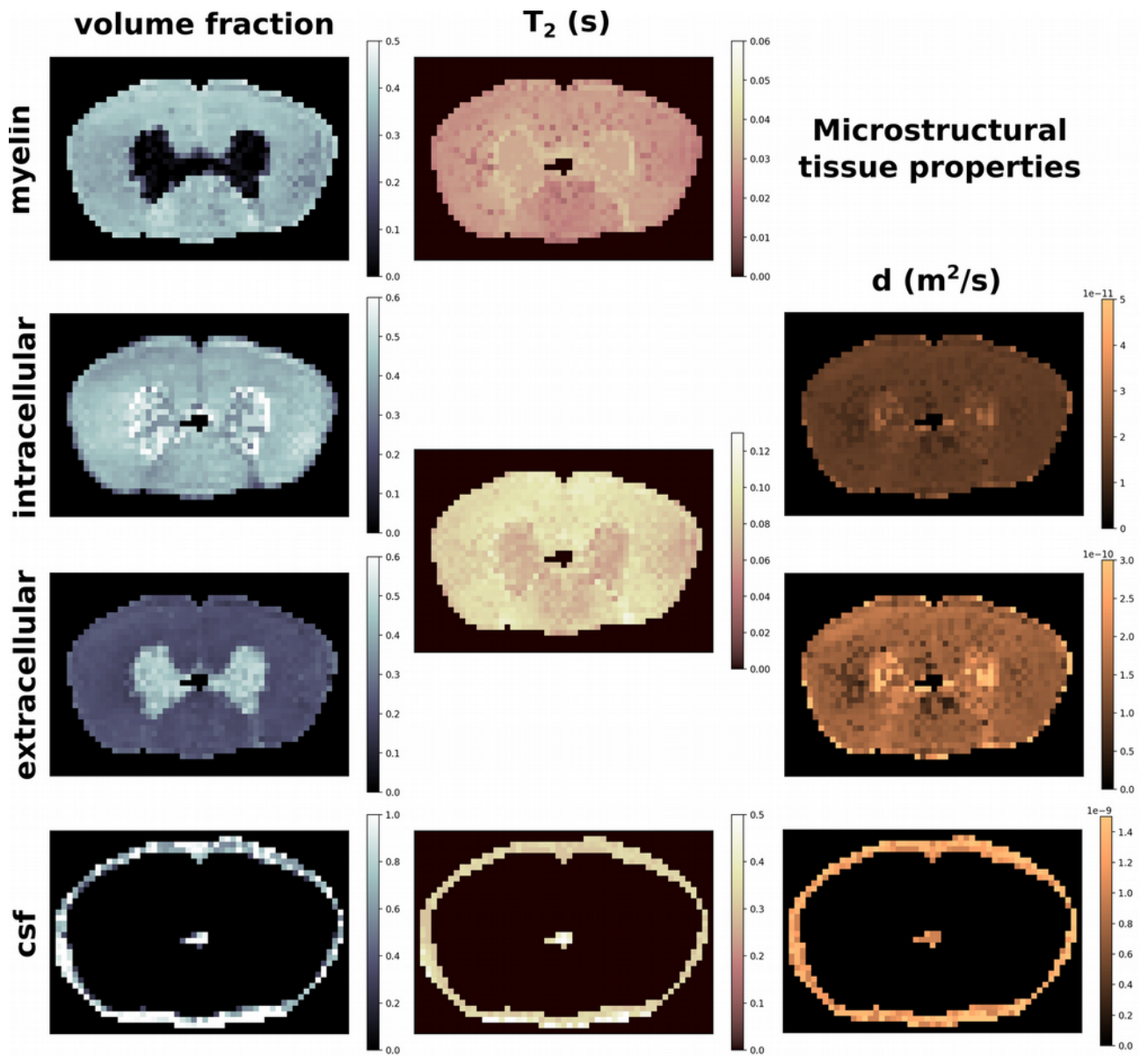
In this work we presented a *novel* multimodal approach to infer microstructure properties by means of a *joint estimation* of diffusometry and relaxometry data acquired in an experimental setup. Results are compelling, and their validation by means of histological data is currently ongoing. Nonetheless, the proposed method has the potential to be very useful for microstructure investigation, and it will be further improved, for instance, by adopting a more robust estimation procedure that will possibly allow disentangling additional properties of the tissue microstructure.

Acknowledgements

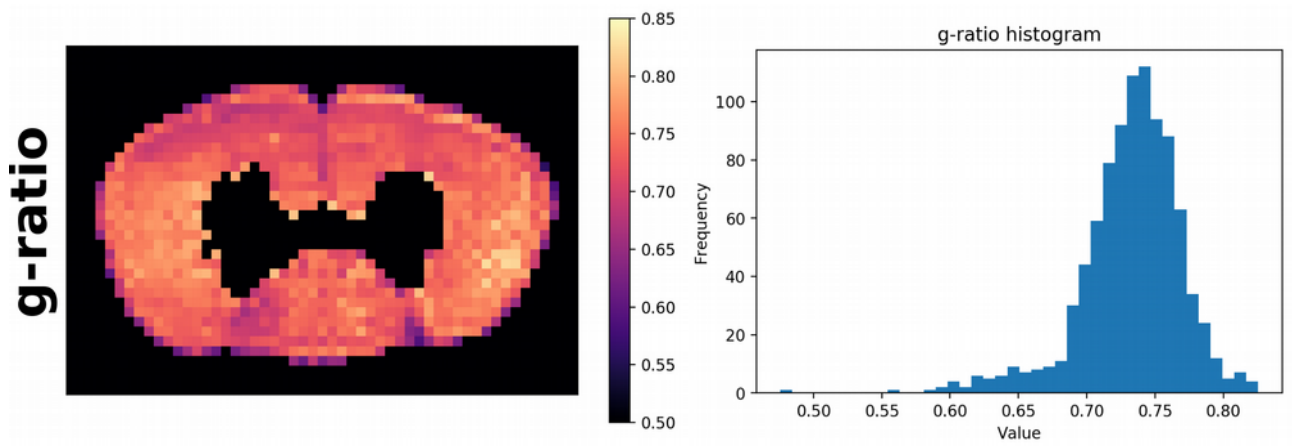
This work is supported by the Swiss National Science Foundation under grant number CRSII5_170873.

References

1. Whittall, K.P., MacKay, A.L.: Quantitative interpretation of NMR relaxation data. *Journal of Magnetic Resonance*, 1989.
2. Stejskal, E.O., Tanner, J.E.: Spin Diffusion Measurements: Spin Echoes in the Presence of a Time Dependent Field Gradient. *JCP*, 1965.
3. Vuong, M.-T., Duval, T., Cohen-Adad, J., Stikov, N., 2017. On the Precision of Myelin Imaging: Characterizing Ex Vivo Dog Spinal Cord with MRI and Histology, in: *Proceedings of the 25th Annual Meeting of ISMRM*. p. 3760.
4. Stikov et al.: In vivo histology of the myelin g-ratio with magnetic resonance imaging. *NeuroImage*, 2015.
5. Chomiak, T., Hu, B.: What is the optimal value of the g-ratio for myelinated fibers in the rat CNS? A theoretical approach. *PloS one*, 2009.



Maps of tissue microstructure properties obtained with the proposed joint estimation method. Columns report the estimated volume fraction, T_2 value, and diffusion coefficient for the compartments reported on the corresponding row. Note that in this work we considered equal the T_2 of the intra- and extracellular compartments. We note that in gray matter the extracellular volume fraction is higher than in white matter, as expected. Moreover, myelin is almost absent in gray matter. Maps generally confirm expected values also for the transverse relaxation time and the diffusion coefficient. Please refer to colorbars to better appreciate the extents of reported values.



G-ratio map estimated with the proposed proposed joint estimation method, based on myelin and intracellular volume fraction maps reported in Fig. 1. Note that the histogram reports values within the reference in literature⁵.